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Chemotherapy-induced painful neuropathy: pain-like behaviours in rodent models and their response to commonly-used analgesics

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Chemotherapy-induced painful neuropathy: pain-like behaviours in rodent models and their response to commonly-used analgesics

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Abstract

Purpose of review: Chemotherapy-induced painful neuropathy (CIPN) is a major dose-limiting side-effect of several widely used chemotherapeutics. Rodent models of CIPN have been developed using a range of dosing regimens to reproduce pain-like behaviours akin to patient-reported symptoms. This review aims to connect recent evidence-based suggestions for clinical treatment to preclinical data.

Recent findings: We will discuss CIPN models evoked by systemic administration of taxanes (paclitaxel and docetaxel), platinum-based agents (oxaliplatin and cisplatin), and the proteasome-inhibitor - bortezomib. We present an overview of dosing regimens to produce CIPN models and their phenotype of pain-like behaviours. In addition, we will discuss how potential, clinically-available treatments affect pain-like behaviours in these rodent models, relating those effects to clinical trial data wherever possible. We have focussed on anti-depressants, opioids and gabapentinoids given their broad usage.

Summary: This review outlines the latest description of the most-relevant rodent models of CIPN enabling comparison between chemotherapeutics, dosing regimen, rodent strain and gender. Preclinical data supports many of the recent suggestions for clinical management of established CIPN and provides evidence for potential treatments warranting clinical investigation. Continued research using rodent CIPN models will provide much needed understanding of the causal mechanisms of CIPN, leading to new treatments for this major clinical problem.

Keywords:

Paclitaxel, oxaliplatin, bortezomib, chemotherapy-induced neuropathy, neurotoxicity

Introduction

Chemotherapy-induced painful neuropathy (CIPN) is a major dose-limiting side effect of several first-line chemotherapeutic agents, affecting up to 70% of patients following standard chemotherapy regimens [1-6]. Patients describe a range of predominantly sensory, bilateral symptoms in both hands and feet (also described as a stocking and glove distribution) including numbness, tingling, ongoing/spontaneous pain, hypersensitivity to mechanical and/or cold stimuli. Patients may find their neuropathy significantly impacts their daily activities, for example difficulty in buttoning up their shirt due to lack of fine touch sensation and/or unable to remove items from a fridge/freezer due to cold hypersensitivity. Pain and sensory abnormalities can persist for months or years following the cessation of chemotherapy. Therefore patients may well be cancer-free, but suffering a debilitating painful neuropathy as a result of their cancer treatment [1, 7, 8]. There is no effective therapy for the prevention of CIPN and only one drug has been recommended for the treatment of established CIPN [9]. Currently, the emergence of CIPN results in dose reduction or cessation, thus potentially impacting on patient survival, as well as quality of life. CIPN is commonly observed following treatment with chemotherapeutics that have different mechanisms of anti-cancer actions; platinum agents, vinca alkaloids, taxanes, thalidomide, proteasome inhibitors and epothilones, reviewed in [10]. The first systemic review and meta-analysis of CIPN prevalence following the end of chemotherapy with paclitaxel, bortezomib, cisplatin, oxaliplatin, vincristine and thalidomide (solo or combination) treatment was recently reported [11]. CIPN was observed in 68.1%, 60%, and 30% of patients, within the first month, at 3 months, and at ≥ 6 months, respectively, after cessation of chemotherapy [11].

In this review, we aim to summarise the studies which have examined rodent models where pain-like behaviours were induced by taxanes, platinum agents or bortezomib. Developing animal models of CIPN which replicate all the symptoms that patients report is somewhat challenging because numbness, tingling and ongoing pain all rely on verbal report from the patient. Thus, most studies have focussed on measuring evoked pain behaviours, although investigation into novel measures of ongoing pain in rodents is an emerging area. In this review, we also aim to discuss the effects - in these rodent models of CIPN - of agents recently suggested as potential treatments for established CIPN in patients [9] namely anti-depressants, opioids and gabapentinoids.

Animal models of CIPN

Taxanes

Paclitaxel and docetaxel are first-line treatments alone or in combination for solid tumours such as breast, ovarian, prostate and non-small cell lung carcinomas. Paclitaxel, a taxane-derived chemotherapeutic, binds to β -tubulin of microtubules [12], stabilizing microtubules and interfering with spindle-microtubule dynamics, arresting mitosis and inducing apoptosis [13]. Docetaxel works via a similar anti-cancer mechanism albeit with different potencies [14] and has been associated with higher levels of neurotoxicity compared to paclitaxel treatment in metastatic breast cancer patients [15]. Initial work investigating the neurotoxicity associated with paclitaxel involved direct application of paclitaxel to peripheral nerves resulting in degeneration and specific aggregation of microtubules [16-18]. However, the relevance of such local application of chemotherapy to understanding mechanisms of CIPN that are evoked by systemic administration is limited due to the high endoneurial concentration. In later studies, rodent models of paclitaxel-induced painful neuropathy were developed using systemic paclitaxel administered via intravenous or intraperitoneal routes (see Table 1). The majority of regimens for paclitaxel and other

chemotherapeutics do not dose animals every day but have a break between each administration in order to mimic cycles of chemotherapy.

Comparison of the integrity of peripheral nerves following different dosing regimens of paclitaxel indicates that degeneration is dose-dependent, with greater degrees of degeneration caused by larger cumulative doses of paclitaxel [23, 30-33]. Systemic administration of low-doses of paclitaxel did not markedly affect neural microtubule structure or cause aggregation as observed following epineural administration [32]. The dose-dependent effects of paclitaxel administration have also been observed in patients, where the incidence and severity of neuropathic signs and symptoms increased with increasing cumulative doses of paclitaxel [34]. Table 1 summarises the evoked pain-like behaviours observed in rodents following different administration schedules of paclitaxel. A range of pain-like behaviours are evoked by low-dose (<10mg/kg) systemic paclitaxel with both mechanical and cold allodynia observed in rats [19, 20] and mice [27]. At higher doses, heat hypoalgesia and motor deficit have been observed, which is likely indicative of pronounced neurodegeneration [23, 24, 35, 36]. Recent preclinical studies have typically utilised low-dose paclitaxel model consisting of four intraperitoneal injections of 1-2mg/kg paclitaxel on alternate days. Such doses do not adversely affect animal health and normal weight gain is observed. Fewer preclinical studies have investigated the painful neuropathy associated with docetaxel treatment. However, similar to paclitaxel, hypersensitivity to mechanical and thermal stimuli is observed at lower doses [28] and heat hypoalgesia is evoked with high cumulative doses of docetaxel [29].

Platinum Agents

Cisplatin was the first inorganic anti-tumour agent and the template for future platinum chemotherapeutics. Cisplatin is used in the treatment of solid tumours including cervical, testicular, non-small cell lung, bladder, head and neck cancers. Oxaliplatin is a first-line and adjuvant treatment for colorectal cancer, and also used in the treatment of oesophageal and stomach cancer. Both agents react with DNA forming inter-/intra-strand platinum-DNA crosslinks, blocking DNA replication/transcription and inducing apoptosis [37, 38]. Table 2 describes rodent models of painful neuropathy induced by systemic administration of platinum-containing chemotherapeutic agents. Here we will discuss oxaliplatin and cisplatin models and observations of induced pain-like behaviours and motor deficits. We did not find any reports assessing pain-like behaviours in rodent models of carboplatin-induced painful neuropathy. The distinct conditions of acute and chronic pain-like behaviours are modelled in both mice and rats by giving a single or repeated doses of platinum-based chemotherapy. Generally, these models are well tolerated with only slight impairment of weight gain. However, as the cumulative dose increases more adverse effects are observed. A number of groups have used transgenic mice [40, 43, 45, 76], although description of these genes is outside the scope of this review. Most studies have used male rodents. However, one study compared the effect of gender on development of cisplatin-induced mechanical hypersensitivity finding more persistence in male mice [77]. Interestingly, one group has modelled neuropathy evoked by combined cisplatin- and paclitaxel- treatment in rats which also had an implanted subcutaneous tumour [73, 78]. Typically most models of CIPN involve the solo administration of a given chemotherapeutic in the absence of tumour load.

All acute oxaliplatin models show a rapid onset of both cold and mechanical allodynia that persists for more than one week following treatment (see Table 2). These symptoms are analogous to the clinical problem where patients most frequently report sensitivity to cold/mechanical stimuli soon after drug

administration. There are many studies investigating chronic oxaliplatin-induced peripheral neuropathy that have used varying doses and regimens of chemotherapy administration (see Table 2). All models showed sustained cold and/or mechanical allodynia that lasted for a number of months. Some studies also reported mechanical hyperalgesia but, like the acute models, heat hyperalgesia reports are conflicting which cannot be attributed to differences in individual/cumulative dose. The majority of cisplatin models of CIPN are chronic. However, a single dose of cisplatin evoked mechanical allodynia and heat hyperalgesia, but not cold allodynia [39]. With repeated dosing, animals consistently develop mechanical allodynia but with mixed outcomes for cold allodynia and heat hyperalgesia (see Table 2). Some studies have investigated whether platinum treatment affects motor as well as sensory function. There are reports of decreased locomotor activity, yet no change in muscle strength in oxaliplatin models [62, 65, 66]. Cisplatin models have shown some reports of decreased locomotor activity and altered gait at high cumulative doses of cisplatin [65, 78] whereas no change in other studies [73, 79].

Bortezomib

Bortezomib (Velcade®) is a boronic acid dipeptide and the first member of a new class of chemotherapeutic agents known as proteasome inhibitors. Bortezomib reversibly binds and inhibits the 26S subunit of the proteasome, disrupting critical cell signalling pathways leading to apoptosis [82]. Unlike other chemotherapeutics, the effects of proteasome inhibition are more pronounced in malignant cells compared to normal cells, with bortezomib sensitising malignant cells to apoptosis, reviewed in [83]. Bortezomib is primarily used as a first-line therapy in the treatment of newly diagnosed and relapsed multiple myeloma [84], but may also be effective in treatment of solid tumours such as ovarian, renal and prostate carcinomas [85, 86]. Table 3 describes rodent models of painful neuropathy induced by systemic administration of bortezomib. Mechanical allodynia and hyperalgesia was commonly reported in both rats and mice. Cold allodynia was quantified in two rat models [89, 91] but not present in mouse models [87, 94]. Heat hyperalgesia has been observed in patients treated with bortezomib [96], however assessment in rodent models has yet to positively report bortezomib-induced heat hyperalgesia (see Table 3).

High doses of bortezomib were associated with heat hypoalgesia and motor deficit in mice [95]. However motor deficits were not found in several other studies [88, 89], although one mouse model reported altered gait following bortezomib [88]. Studies in rats and mice reported that weight gain was impaired by bortezomib compared to vehicle-treated animals [92, 94]. Clinically, bortezomib is administered via intravenous or subcutaneous routes. However, subcutaneous administration had reduced and/or delayed incidence of peripheral neuropathy, without a loss in efficacy or survival rates [97-100] and is preferable to patients [101]. More preclinical research on the effect of route of administration on bortezomib-induced pain-like behaviours would be interesting.

Effects of clinically available analgesics in rodent models of CIPN

A recent review of the randomized controlled trials (RCTs) in CIPN patients aimed to produce evidence-based guidance for CIPN treatments [9]. A moderate recommendation was made for duloxetine. The panel suggested that other drugs, e.g. gabapentin, may be offered on the basis of their use in other neuropathic pain conditions and in light of the very limited treatment options for CIPN [9]. In this review, we will discuss the reported effects of commonly-used analgesics for chronic pain in the rodent models of CIPN. Typically, the lack of analgesic drug effects in rodents are not as readily published as observed analgesic effects in rodents. Therefore it is not entirely accurate to directly compare a lack of effect observed in clinical trials to

preclinical work, given this publication bias. Given space constraints we have focussed on anti-depressants, opioids and gabapentinoids and are unable to cite all preclinical studies that show similar effects.

Anti-depressants

Duloxetine significantly decreased average pain scores, numbness and tingling compared to placebo in CIPN patients [102]. Interestingly, patients with CIPN evoked by oxaliplatin responded better to duloxetine treatment than paclitaxel-treated CIPN patients [102]. Oral administration of duloxetine inhibited chemotherapy-induced mechanical allodynia in paclitaxel-treated mice and bortezomib-treated rats at 30-100mg/kg doses [89, 103]. Recently, pain investigators have started to develop methods of measuring ongoing pain as opposed to evoked hindpaw withdrawal responses to mechanical or cold stimuli. Thermal place preference has shown that oxaliplatin-treated animals avoid cold temperatures [71], which can be overcome by duloxetine [50].

A small trial of amitriptyline in CIPN patients found no significant change in pain scores compared to placebo [104]. However, there was a trend to improved quality of life measures in amitriptyline-treated CIPN patients [104]. Topical treatments containing amitriptyline have been examined in two placebo-controlled RCTs [105, 106]. Topical application of 4% amitriptyline and 2% ketamine cream twice daily, had no effect on pain and numbness scores, in taxane and non-taxane derived CIPN [105]. A trend towards improved sensory neuropathy was seen in CIPN patients following topical application of a baclofen/amitriptyline/ketamine combination [106]. Given the lack of toxicity and systemic adsorption, further trials utilising higher dosing regimens of this combination could be promising. As these topical treatments are drug combinations, it is not possible to attribute beneficial effects to a specific drug. Several preclinical studies have assessed the effects of amitriptyline in CIPN. In a repeated dosing paradigm, the effects of daily intraperitoneal injections of amitriptyline on established paclitaxel-induced mechanical hypersensitivity in rats were assessed for four days [107]. Anti-nociceptive effects were only observed 24 hours after the second dose and then following remaining doses [107]. In oxaliplatin models, intraperitoneal amitriptyline had no effect on acute cold allodynia [44]. However, daily oral amitriptyline prevented the development of chronic hypersensitivity to cold and mechanical stimuli [68]. Perhaps suggesting that analgesic effects of amitriptyline on CIPN are only observed with repeated dosing. Indeed, a single oral dose of amitriptyline had no effect on mechanical allodynia induced by bortezomib [89] or cisplatin [108].

A small-scale clinical study showed that venlafaxine was analgesic in chronic CIPN evoked by oxaliplatin [109]. In addition, venlafaxine reversed established oxaliplatin-induced cold allodynia in rats [66]. Milnacipran is another clinically-available anti-depressant, also used for treatment of fibromyalgia, which could be a promising candidate for the treatment of CIPN. In mice, milnacipran prevented acute oxaliplatin-induced cold allodynia [44], inhibited established oxaliplatin-induced mechanical allodynia [42] and inhibited paclitaxel-induced mechanical allodynia with repeated dosing [110].

Opioids

We did not find any clinical trials on the use of morphine, oxycodone, fentanyl or tramadol in CIPN patients. However, systemic morphine is used as a positive control in preclinical studies assessing potential analgesics and efficacy has been demonstrated with the others. Morphine inhibited paclitaxel-induced mechanical hypersensitivity, but typically only at high doses (>5mg/kg) [20, 111, 112]. Morphine reversed

cisplatin-induced cold allodynia [80] as well as both acute and chronic cold allodynia evoked by oxaliplatin [52, 66]. Morphine also inhibited cisplatin- and oxaliplatin-induced mechanical hypersensitivities [58, 108, 113]. Oxycodone is reported to reverse paclitaxel- and oxaliplatin-induced mechanical allodynia, but mixed results are reported with fentanyl administration [58, 59]. Finally, tramadol (10-20mg/kg) administration had similar inhibitory effects on pain-like behaviours evoked by paclitaxel [107], oxaliplatin [44] and bortezomib [89].

Gabapentinoids

Gabapentin administration did not improve pain scores of patients with taxane-/platinum-derived CIPN in a RCT against placebo [114]. In preclinical studies, gabapentin is often used as a positive control to assess potential analgesics. Gabapentin (100mg/kg) only reduced paclitaxel-induced mechanical hypersensitivity in rats with repeated dosing [115]. Interestingly, gabapentin was recently shown to attenuate paclitaxel-induced gait alterations [116]. Gabapentin prevented acute cold allodynia in mice [44] and reversed chronic cold allodynia in rats [66] evoked by oxaliplatin. Effects were also observed in cisplatin-evoked pain-like behaviours, with attenuation of cold allodynia [74] and reduction of mechanical allodynia in mice of both genders [77] and in rats [108]. In addition, conditioned place preference showed cisplatin-treated animals spent more time in an environment associated with gabapentin administration [76]. Two small-scale studies have shown pregabalin administration was effective in CIPN caused by oxaliplatin [117, 118]. Preclinical studies assessing pregabalin are more limited. However, pregabalin has been shown to inhibit several pain-like behaviours evoked by paclitaxel [103], docetaxel [28], oxaliplatin [52] and bortezomib [89].

Conclusion

Compared to other chronic pain conditions, differential analgesic effects are observed in both CIPN patients and rodent models. This suggests different causal mechanisms for CIPN which may or may not be identical for all chemotherapeutics that evoke pain. Continued research using the many available rodent models will provide much needed mechanistic understanding of the causal mechanisms of CIPN, leading to new treatments for this major clinical problem.

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Table 1: Summary of dose administration and pain-like behaviours in rodent models of taxane-induced painful neuropathy. Only studies which systemically administered paclitaxel or docetaxel and undertook behavioural testing were included. Abbreviations: i.p. intraperitoneal, i.v. intravenous, CA = cold allodynia, HH = heat hyperalgesia, HHO = heat hypoalgesia, MA = mechanical allodynia, MH = mechanical hyperalgesia, q1d = daily, q2d = alternate days, q1w = once per week. Symbols: (+) indicates presence of pain-like behaviour following paclitaxel or docetaxel administration; (-) indicates this behaviour was assessed but not evident following paclitaxel or docetaxel administration.

Regimen	Route	Cumulative Dose	Pain-like Behaviour	Species & gender	Ref
PACLITAXEL					
0.5mg/kg, 1mg/kg or 2mg/kg, q2d x 4	i.p.	2mg/kg, 4mg/kg or 8mg/kg	+MA, +MH, +HA, +CA - motor deficit	Sprague-Dawley rat, ♂	[19, 20]
0.1mg/kg, 0.5mg/kg or 1mg/kg, q1d x 5 days for 2 weeks	i.p.	1mg/kg, 5mg/kg or 10mg/kg	+MH, +MA, +HA	Sprague-Dawley rat, ♂	[21]
16mg/kg or 32 mg/kg x 1 16mg/kg, q1w x 5 weeks	i.p.	16mg/kg, 32mg/kg or 80 mg/kg	+MH, +HHO	Sprague-Dawley rat, ♂	[22]
5mg/kg, q1d x 5 days	i.v.	25mg/kg	+HHO +motor deficit	Wistar rat, ♀	[23]
21.6mg/kg, q1d x 6 days	i.p.	129.6mg/kg	+HHO	CD1 mice ♂	[24]
5mg/kg x 1	i.p.	5mg/kg	+MA	C57BL/6 mice ♂	[25, 26]
1mg/kg, q2d x 4	i.p.	4mg/kg	+MA	Comparison of all "J" sub-strains: 129P3, A, AKR, C3H/He, C57BL/6, C57BL/10, CBA, DBA/2, RIIS, SM mice, ♂ and ♀	[27]
1mg/kg, q2d x 4	i.p.	4mg/kg	+CA -HA	DBA/2 mice, C57BL/6 mice, ♂ and ♀	[27]
DOCETAXEL					
10mg/kg x 1	i.v.	10mg/kg	+MA, +MH, +HH, +CA	Sprague Dawley rat, ♂	[28]
10mg/kg, q1w, x 4 weeks	i.v.	40mg/kg	+HHO	Fischer rat, ♂	[29]

Table 2: Summary of dose administration and pain-like behaviours in rodent models of platinum-induced painful neuropathy. Only studies which systemically administered oxaliplatin or cisplatin and undertook behavioural testing were included. Abbreviations: i.p. intraperitoneal, i.v. intravenous, CA = cold allodynia, HH = heat hyperalgesia, HHO = heat hypoalgesia, MA = mechanical allodynia, MH = mechanical hyperalgesia, q1d = daily, q2d = alternate days, q1w = once per week, q2w = twice per week, q3w = thrice per week, q4w = 4 times per week. Symbols: (+) indicates presence of pain-like behaviour following oxaliplatin or cisplatin administration; (-) indicates this behaviour was assessed but not evident following oxaliplatin or cisplatin administration.

Regimen	Route	Cumulative dose	Pain Behaviour	Gender/ Species	Reference
Oxaliplatin acute models					
2 mg/kg x 1	i.v.	2 mg/kg	+CA, +HH, +MA, +MH	Sprague-Dawley rats ♂	[39, 40]
3 mg/kg x 1	i.p.	3 mg/kg	+CA, +MA	C57BL/6 mice ♂	[40-42]
5 mg/kg x 1	i.p.	5 mg/kg	+CA, +MA	C57BL/6 mice ♂	[43, 44]
1, 3, or 6 mg/kg x 1	i.p.	1, 3, or 6 mg/kg	+CA, +MA	C57BL/6 mice ♂	[45, 46]
10 mg/kg x 1	i.p.	10 mg/kg	+CA, +MA	ddY mice ♂	[47]
10 mg/kg x 1	i.p.	10 mg/kg	+CA, +HH, +MA	CD-1 mice ♂	[48]
3, 6 or 12 mg/kg x 1	i.p.	3, 6 or 12 mg/kg	+CA, +MA -HH	Sprague-Dawley rats ♂	[49-52]
Oxaliplatin chronic models					
2 mg/kg q2d x 4	i.p.	8 mg/kg	+MA	Sprague-Dawley rats ♂	[53]
1 mg/kg q2w x 4.5 weeks	i.v.	9 mg/kg	+MA	Swiss mice ♂	[54]
2 mg/kg q1d x 5	i.p.	10 mg/kg	+CA, +MA - HH	Sprague-Dawley rats ♂	[55, 56]
5 mg/kg q3w x 1 week	i.p.	15 mg/kg	+MA	Sprague-Dawley rats ♂	[57]
2 mg/kg q2w x 4 weeks	i.p.	16 mg/kg	+MA	Sprague-Dawley rats ♂	[58, 59]
0.6, 2 or 6mg/kg q1w x 3 weeks	i.p.	1.8, 6 or 18 mg/kg	+MH	Wistar rats ♂	[60]
3 mg/kg day 1, 3, 5, 8, 11 and 15	i.p.	18 mg/kg	+MH	Wistar rats ♂	[61]
2 mg/kg q2w x 4.5 weeks	i.p.	18 mg/kg	+CA, +MA, +MH - Motor deficit	Wistar rats ♂	[62]
A. 0.5, 1, 2, or 5 mg/kg x 1 B. 5 mg/kg q1w x 4 weeks	i.v.	A. 0.5, 1, 2, or 5 mg/kg B. 20 mg/kg	+CA, +HH, +MA,	Sprague-Dawley rats ♂	[63]
3.5 mg/kg q2w x 4 weeks	i.v.	28 mg/kg	+CA, +MA - HH	BALB/c mice ♀	[64]
3mg/kg q1d x 5 for 2 cycles, with 5 day break	i.p.	30 mg/kg	+CA, +MA, +motor deficit - HH - grip strength deficit	C57BL6J mice ♂	[65]
1, 2 or 4 mg/kg, q2w x 4.5 weeks	i.v.	9, 18 or 32 mg/kg	+CA, +HH, +MA, +MH, +grip strength deficit - motor deficit	Sprague-Dawley rats ♂	[66]

4 mg/kg q2w x 4 weeks	i.p.	32 mg/kg	+CA, +MA	Sprague-Dawley rats ♂	[59, 67-70]
2 or 4 mg/kg q2w x 4 weeks	i.p.	16 or 32 mg/kg	+MA	Sprague-Dawley rats ♂	[67]
A. 15 mg/kg x 1 B. 15 mg/kg q1w x 3 weeks	i.p.	A. 15 mg/kg B. 45 mg/kg	+CA, +MA	BALB/c mice ♂	[71]
Cisplatin models					
2 mg/kg x 1	i.v.	2 mg/kg	+HH, +MA - CA	Sprague-Dawley rats ♂	[39]
0.1, 0.5, or 1 mg/kg q2d x 3	i.p.	0.3, 1.5 or 3 mg/kg	+HH, +MA	Sprague-Dawley rats ♂	[72]
3 mg/kg q1w x 2 weeks	i.p.	6 mg/kg	+HHO - motor deficit	Dark agouti rats ♀	[73]
3 mg/kg q1w x 3 weeks	i.p.	9 mg/kg	+CA, +MA - HH	Sprague-Dawley rats ♂	[74]
1 or 2 mg/kg q1w x 5 weeks	i.p.	5 or 10 mg/kg	+MA	Wistar rats ♂	[75]
2.3 mg/kg q2d x 6	i.p.	13.8 mg/kg	+MA	C57BL/6 mice ♂ +♀	[76, 77]
2 mg/kg q2w x 4 weeks	i.p.	16 mg/kg	+HHO, +motor deficit	Dark agouti rats ♀	[78]
2 mg/kg q2w x 4.5 weeks	i.p.	18 mg/kg	+HH - Motor deficit	Wistar rats ♀	[79]
5 mg/kg q1w x 4 weeks	i.p.	20 mg/kg	+CA, +MA	C57BL6J mice, gender not specified	[80]
A. 3 mg/kg q1w x 5 weeks B. 2 mg/kg q2w x 5 weeks C. 1 mg/kg q3w x 5 weeks	i.p.	A. 15 mg/kg B. 20 mg/kg C. 15 mg/kg	+CA, +MA - motor deficit	Sprague-Dawley rats ♂	[81]
2.3 mg/kg q1d x 5 for 2 cycles, with 5 day break	i.p.	23 mg/kg	+MA, +HH, +motor deficit - CA - grip strength deficit	C57BL6J mice ♂	[65]

Table 3. Summary of dose administration and pain-like behaviours in rodent models of bortezomib-induced painful neuropathy. Only studies which systemically administered bortezomib and undertook behavioural testing were included. Abbreviations: i.p., intraperitoneal, i.v., intravenous, s.c., subcutaneous, CA = cold allodynia, HH = heat hyperalgesia, HHO = heat hypoalgesia, MA = mechanical allodynia, MH = mechanical hyperalgesia, q1d = daily, q2w = twice per week, q3w = thrice per week, q4w = 4 times per week. Symbols: (+) indicates presence of pain-like behaviour following bortezomib administration; (-) indicates this behaviour was assessed but not evident following bortezomib administration.

Regimen	Route	Cumulative Dose	Pain Behaviour	Species & gender	Reference
0.03-0.3 mg/kg x 1	i.v.	0.03-0.3 mg/kg	+MA, +MH -CA, -HH	C57BL/6NCr mouse, ♂	[87]
0.4mg/kg, q3w x4 weeks	i.p.	4.8 mg/kg	+MA, +gait alteration, +reduced open field movement - Motor deficit	C57Bl/6J mouse, ♂	[88]
0.05, 0.1 or 0.2 mg/kg, q2w x2 weeks	i.p.	0.2, 0.4 or 0.8 mg/kg	+MA, +CA -HH, -motor deficit	Sprague Dawley rat, ♂	[89]
0.15 mg/kg, q4w	i.p.	0.6 mg/kg	+MH -HH, -CA, -motor deficit	Sprague Dawley rat, ♂	[90]
0.2mg/kg, q1d x5 days	i.p.	1 mg/kg	+MA, +MH, +CA -HH	Sprague Dawley rat, ♂	[91]
0.15 mg/kg or 0.2 mg/kg, q3w, x8 weeks	i.v.	3.6 or 4.8 mg/kg	+MA -HH	Wistar rat, ♀	[92]
0.2 mg/kg, q3w, x8 weeks	i.v.	4.8 mg/kg	+MH -HH	Wistar rat, ♀	[93]
0.8 mg/kg, q2w, x4 weeks	i.v.	6.4 mg/kg	+MH -HH, -CA	Balb/c mouse, ♀	[94]
1.0 mg/kg, q2w, x6 weeks	s.c.	12 mg/kg	+HH, +motor deficit	Swiss OF1 mouse, ♀	[95]